## Section I (Remarks)

### Rejection of Claims 1, 5, 8, 9 and 11 Under 35 USC 102(b) Over Kim et al.

In the June 9, 2009 Office Action, claims 1, 5, 8, 9 and 13 were rejected under 35 USC 102(b) over Kim et al. WO96/30390 ("Kim"). This rejection is respectfully traversed.

Claim 1 of the present application recites:

*"1. A process for purifying 17a-acetoxy-llfJ-(4-N,N-dimethylaminophenyl)-19norpregna-4,9-diene-3,20-dione (VA-2914) comprising recrystallising raw (VA2914) in isopropanol and forming (VA-2914) isopropanol hemisolvate."*

Recrystallization is a typical procedure in chemistry for purifying compounds. It allows one to separate compounds with different solubility properties in a given solvent or mixture of solvents. By controlling the conditions, the solubility difference can be used to recrystallize a substance. Recrystallization is based on the fact that every molecule has a specific saturation point in each solvent. Therefore, a saturated solution can be prepared and, if the saturation point is overcome (by cooling down, evaporating the solvent, changing the polarity of the solution, etc), the solvent will be unable to contain the solute, and the solute will therefore precipitate as a solid. Under suitable conditions, the solute might precipitate to form an ordered arrangement, thus forming a crystal lattice. The recrystallized solid is then filtered away from the liquid (mother liquor). All the impurities which are more soluble will remain in the mother liquor after the desired compound has recrystallized and therefore further filtration will allow to purify the compound from said impurities.

There are different recrystallization techniques. However, they all include the following common steps:

1. Dissolving the solute.
2. Crystallizing the solute.
3. Separating the resulting crystals.

In the present application, recrystallization of raw VA-2914 from isopropanol gives rise to the formation of VA-2914 isopropanol hemisolvate crystals. All the steps followed to perform the recrystallization are detailed on page 5 of the originally filed application, including, of course, the three basic steps mentioned above.

Example 2 of the INSTANT application refers to a specific embodiment wherein the solute is dissolved in isopropanol at high temperature, crystals were formed by cooling down the solution and, finally, crystals were collected by filtration. In contrast, according to example 7, page 23, the process followed by Kim et al. is as follows:

> *"The above syrup was dissolved in 300 mL of isopropyl alcohol and evaporated. The dissolution and evaporation was repeated three times. Finally, the remaining solid, which retained isopropyl alcohol as solvent of recrystallization, was dissolved in ethyl acetate and evaporated to give a stable foam. The foam was quickly dissolved in ether, and this solution was set aside to crystallize. The solid that formed was collected byfiltration, wash with ether, and dried .... "*

That is, the process disclosed by Kim et al. only comprises the steps of dissolving the raw material in isopropanol, followed by evaporation. Therefore, it does not include the essential steps of a recrystallization procedure and, therefore, it is not a recrystallization, but a dissolution-evaporation process. As a consequence, it does not allow one to purify the compound from impurities with different solubility, since no separation of the resulting solid from impurities with different solubility is performed.

This type of dissolution-evaporation process are usually employed to remove low boiling point impurities or rest of solvents previously employed. This way, addition of a solvent with a higher boiling point (as isopropanol) will help to drag volatile impurities during its evaporation. Indeed, it can be considered as a distillation process, but never as a recrystallization process. Only low boiling point contaminants will be separated. However, solid impurities, and even any impurities with a boiling point higher than isopropanol, will necessarily be part of the remaining solid.

The fact that Kim et al. state that *"the remaining solid, which retained isopropyl alcohol as solvent ofrecrystallization, ...* " is irrelevant, since no recrystalization has been carried out. The remaining solid may contain retained isopropanol within the remaining residue. The skilled person reading Kim et al. would never have recrystallized the raw material in isopropanol, but rather, would simply have dissolved and evaporated the resulting solution as disclosed in Example 7.

In addition, on page 15, lines 19-23, *Kim* et al. disclose that:

> *"the compound of formula I can be purified by crystallization from ether in high yield and high purity (m.p.: 183-185°C)".*

Kim does not disclose or suggest using isopropanol as a recrystallization solvent. In this sense, and as mentioned above, the procedure described by Kim et al. recites as follows:

> *"The above syrup was dissolved in 300 mL of isopropyl alcohol and evaporated. The dissolution and evaporation was repeated three times. Finally, the remaining solid, which retained isopropyl alcohol as solvent of recrystallization, was dissolved in ethyl acetate and evaporated to give a stable foam. The foam was quickly dissolved in ether, and this solution was set aside to crystallize. The solid that formed was collected by filtration, wash[ed] with ether, and dried ....* "

That is, the recrystallization from ether is clearly disclosed through the description of the essential steps of a recrystallization process described above. It is therefore clear that the process disclosed by Kim et al. consists of a dissolution-evaporation stage (distillation) in isopropanol, a dissolution-evaporation stage in ethyl acetate and a recrystallization stage from ether. However, said process does not comprise a recrystallization stage from isopropanol. Consequently, the process of Kim et al. does not encompass the process of current claim 1, which is therefore new over Kim et al.

Accordingly, the rejection of claim 1 should be withdrawn.

Claims 5 and 8 include the recrystallization stage from isopropanol and, therefore, are also new. Accordingly, the novelty rejection of claims 5 and 8 should be withdrawn.

Claim 9, defining VA-2914 isopropanol hemisolvate, complies with the novelty requirement as well. As stated above, the process of Kim et al. does not disclose VA-2914 isopropanol hemisolvate, but rather, a residue after distilling the raw material. Indeed, Kim does not even mention forming crystals. Accordingly, the novelty rejection of claim 9 should be withdrawn.

Instant claim 13 refers to a method of producing VA-2914 that comprises providing its isopropanol hemisolvate. Once again, Kim et al. do not disclose VA-2914 isopropanol hemisolvate. Therefore, the claimed method of producing VA-2914 using the isopropanol hemisolvate is necessarily new over Kim et al. Accordingly, the novelty rejection of claim 13 should be withdrawn.

Finally, the Examiner considered (page 3, fourth paragraph of the Office Action) that, according to Example 2 of the instant application, the isopropanol hemisolvate obtained is a cake and not crystals. Applicants respectfully disagree.

A "cake" (or "filter cake") is a common term used to refer to the solid that is retained in the funnel during filtration process, in opposition to the filtrate, which refers to the solution coming through the filter.

The term "cake" is generally used independently of the nature of the solid particles forming it. As mentioned along the whole application, the process of the invention provides VA-2914 isopropanol hemisolvate crystals. Therefore, it is obvious that the cake referred to in Example 2 of the application is a cake formed by hemisolvate crystals. Even more, as mentioned on said example (lines 23-24) the hemisolvate obtained was characterized by X-ray diffraction, a technique that can only be used to study crystalline structures.

For at least these reasons, Applicants respectfully request that the Examiner withdraw the rejections of claims 1, 5, 8, 9, and 13 under 35 U.S.C. 102 (b).

**Rejections under 35 USC 103(a)**

The rejection of claims 2-4, 6, 7, 10 and 12 under 35 U.S.C. 103 (a) over Kim et al., as applied to Claims 1, 5, 8 and 9, above, and, further in view of Cook et al. (WO 99/45022), was maintained from the previous Office Action. The rejection of claims 14 and 15 under 35 U.S.C. 103 (a) over Kim et al., as applied to Claims 1, 5, 8 and 9, above, and, further in view of Cook et al. (WO 99/45022), was also maintained from the previous Office Action. Applicants respectfully traverse these rejections.

As discussed above, the process disclosed by Kim et al. is different from that of the claimed invention. Kim et al. teach purifying raw VA-2914 by a dissolution-evaporation stage in isopropanol, followed by a dissolution-evaporation stage in ethyl acetate and a final recrystallization stage from ether. In contrast, the present invention refers to purification of raw VA-2914 through recrystallization from isopropanol followed by recrystallization from ether or ethanol/water. Therefore, the process of the present invention differs from that of Kim et al. in the use of an intermediate recrystallization step from isopropanol, thus providing VA-2914 isopropanol hemisolvate.

Applicants have surprisingly found that the isopropanol hemisolvate presents some specific solubility properties (lower solubility) that allow a better separation from the impurities through recrystallization. As a consequence, the whole process affords

VA-2914 with an improved purity. The question then, is to determine whether this step would have been obvious for the skilled artisan in view of the prior art.

As previously mentioned, Kim et al. do not teach or even suggest the possibility of performing a previous recrystallization from isopropanol. It would have never been obvious for the skilled person, in searching for a new method to purify VA-2914, to include a previous step of recrystallizing the raw material from isopropanol. In addition, the process of the invention is not just a mere alternative to purifying VA-2914, but an inventive one. As stated in the application, the process of the invention provides an improved purity. Such improvement was demonstrated by the color and the melting point of the final product.

The Examiner considers that the difference observed between the melting points (189°C vs. 183-185°C) is not significant. We strongly disagree. Melting point is one of the oldest test methods to ascertain purity of organic compounds. The melting point determination is an easy, fast and cost-effective technique still used for gauging purity of organic and pharmaceutical compounds. It is well-known that the melting point of a pure substance is always higher than the melting point of an impure sample of that particular substance.

Mixtures of substances also show a melting range instead of a sharp melting point, as pure substances. The greater the amount of impurity present, the lower the melting point and the wider the melting range. A pure substance melts at a precisely defined temperature, characteristic of every crystalline substance. Therefore, a difference of 4-6°C in the melting point is quite significant.

Moreover, Kim et al. published a paper *(Steroids 2000,* 65, *395-400),* copy enclosed, where the results of their previous patent were described (see page 396, first paragraph, last sentence - reference [9] refers to the US patent application whose priority is claimed by Kim et al.). In this paper, the synthesis and purification of VA-2914 (compound 8 of the publication) is described in point 2.7. In this case, the intermediate dissolution-evaporation stage of the raw material in isopropanol was replaced by a dissolution-evaporation stage in ethyl acetate. However, a product with a similar melting point as in their previous patent was obtained, thus indicating that the dissolution-

evaporation step in isopropanol did not influence the purity of the final compound. This is in stark contrast to the instantly claimed process, in which the recrystallization step from isopropanol allows one to improve the purity of the product.

In addition, the paper indicates that the final product with a melting point of 183-185°C corresponds to a compound that is only greater than 98% pure. In contrast, the purification process of the invention allows one to prepare material with purity greater than 99.5%, in accordance with the higher melting point observed. A chromatograph showing that the purity degree of said compound (VA2914) is 99.72% is also enclosed.

The Examiner requested comparative experiments wherein the only difference is the method via which the hemisolvate is obtained. However, we submit that the application the process carried out in the application is similar to the one by Kim et al., except from the step where the raw material is treated with isopropanol. The results obtained with the process of the application are shown in Figure 5, which can be compared with product obtained by Kim et al. which purity, as discussed above, is significantly lower. In view of the above, we submit that all the claims of the application are inventive over Kim et al. In addition, the presence of an unexpected result (improved purity) has been demonstrated.

Cook et al. refer to compounds structurally related to VA-2914. However, Cook does not teach using recrystallization to purify the compounds. Therefore, the skilled person in view of this document, either alone or combined with Kim et al., would have never arrived at the process of the invention.

Further, the combination of references does not teach each element of the claims, since neither Cook nor Kim disclose recrystallizing the product from isopropanol. A combination of references cannot render a claimed process obvious if the combination does not teach each element of the claims.

Claim 12, directed to the carbinol acetate, also fulfills the requirements of novelty and non-obviousness, as acknowledged during the International phase of the corresponding PCT application. Neither Kim nor Cook disclose the specific combination of substituents required to arrive at the compound of claim 12. Accordingly, this compound is novel and non-obvious. In addition, this compound has been found to be

useful in the preparation of VA-2914 with an improved purity. Consequently, this compound is a novel and non-obvious intermediate, which can be used in an overall novel and inventive process.

For at least these reasons, Applicants respectfully request that the Examiner withdraw the rejections under 35 U.S.C. 103 (a).

## CONCLUSION

In light of the arguments presented above, it is requested that the rejection of the pending claims be withdrawn, and that the patentability of the pending claims likewise be acknowledged. All of Applicants' pending claims are now patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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